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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,332	02/09/2004	Gary T. Wang	09095.0009-01000	8910

22852 7590 11/01/2005

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EXAMINER	
COPPINS, JANET L	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,332	WANG ET AL.	
	Examiner	Art Unit	
	Janet L. Coppins	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 3-27 are pending in the instant application.

Response to Amendment

1. Receipt is acknowledged of Applicants' Amendment and Response, filed August 5, 2005, which have been reviewed by the Examiner and entered of record in the file.

2. Accordingly, claim 2 has been cancelled and claims 1, 3, 5, 11, 13-15, 17-19, 20, and 22-24 have been amended.

Claim Rejections - 35 USC § 112

3. Claims 1-8 and 10-25 previously rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendments to the claims in order to add R^5 onto the phenyl ring, the Examiner withdraws the rejections.

Claim Rejections - 35 USC § 102

4. Claims 1, 8, 10, 13, 16, and 21, previously rejected under 35 U.S.C. 102(b) as being anticipated by Cox et al, U.S. 4,900,571. In view of Applicants' amendatory changes to the claims in order to specify a pyridine ring in the "R^3" position of formula I, the anticipation rejections have been obviated and are withdrawn.

Claim Objections

5. Claims 2-7, 11, 12, 14, 15, 17-20, and 22-25 previously objected to for being dependent on rejected base claims. Since the Examiner has withdrawn the rejections to said base claims (see above), the claim objections are herein withdrawn.

Rejoinder

6. Claims 1, 3-8, and 10-25 directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 9, 26, and 27, directed to the process of using the product, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Therefore method claims 9, 26, and 27 hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Since all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, the restriction requirement made in the Office action mailed on February 1, 2005, is hereby withdrawn.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9, 26, and 27 rejected under 35 U.S.C. 112, first paragraph, as not being fully enabled. The specification, while being enabling for treating certain diseases that benefit from the inhibition of cell adhesion, does not reasonably provide enablement for treating all of the diseases/disorders encompassed by claims 9, 26 and 27. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Regarding claim 26, while various diseases/disorders may be listed in the specification, the claims are not enabled for *all* disorders ("pathologies") responsive to the interaction of LFA-1 with ICAM-1 or ICAM -3, since there is no indication as to the full range of disorders that

could be treated using the instant claimed method.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, the claims are directed to many disorders and conditions that are not enabled in the specification, including those broadly recited in claims 9, 26, and 27.

The nature of the invention

The nature of claim 9 is the inhibition of inflammation or suppression of immune response, comprising administering the instant claimed compound to a mammal. Claim 26 is directed to a method of "ameliorating a pathology." However, claim 26 is a reach-through claim, drafted in terms of an interaction between molecules, which is not a specific utility such that one skilled in the art would know how to perform the claimed method for treating a specific disease or diseases.

Claim 27 is directed to the treatment of many different types of diseases or conditions that are unrelated, such as autoimmune diseases, inflammatory diseases, tumor metastasis, reperfusion injury, etc.

The state of the prior art and the predictability or lack thereof in the art

It is well recognized in the medical art that treatment of diseases or symptoms are not analogous terms. Furthermore, the diseases of claims 9, 26 and 27 are not the same but different

diseases. Treating "inflammation, autoimmune diseases, inflammatory diseases, allograft rejection, tumor metastasis, etc" encompasses thousands of diseases/conditions, including autoimmune and immunodeficiency diseases, for example MS, AIDS/HIV, SCID, and CFS, of which there is no known cure. Such as all cancer patients require administering a cytotoxic/antitumor agent, on the other hand, treating autoimmune diseases employ the use of immunosupressants.

The immune response of a living organism is a complex, specific and interrelated process. It involves the overall coordination of all the lymphocytes, B-types, T-types, etc., their population, expression and interaction. The intertwined dependency and complexity in bio-feedback control relationships involves enormous biological pathways and physiological homeostasis.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Also, in the absence of a showing of correlation between all the diseases claimed as capable of being treated by the compound of claim 1 and the inhibition of LFA-1mediated cell adhesion, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1.

The amount of direction or guidance present and

the presence or absence of working examples

The specification has enabled only the compounds according to formula (I) that

selectively inhibit the interaction of LFA-1 with ICAM-1 and ICAM-3. Treatment of the claimed distinct disorders/diseases are normally disease or symptom oriented, thus are highly individualized, i.e. treating the symptoms of asthma (sudden recurring attacks of labored breathing, chest constriction, and coughing) would not employ the same methods as treating the symptoms of arthritis (stiffness and joint pain). The efficacy of an individual compound against a specific disease or symptom needs to be specifically and individually supported by factual evidence. Such evidence has not been described or supported by the specification.

The specification also only discusses two *in vitro* inhibition assays on pages 114-115 which demonstrate the ability of the instant compounds to inhibit the binding of LFA-1 to ICAM-1, including a few IC_{50} values. and provides no data for describing the efficacy of the claimed compounds for treating the full scope of disorders that Applicants have claimed. In view of the diversified multiple diseases as claimed, such a single universal disclosure fails to provide specific description in guiding one skilled in the art to pick and choose the specific compounds that would be useful for treating one or a specific group of pathological conditions. The standard of 35 USC 112, first paragraph rejections is that the application *itself* must inform, rather than direct, others to find out for themselves, please see *In re Garnder*, 166 USPQ 138.

The breadth of the claims

In claims 9 and 27, Applicants are claiming a method of inhibiting inflammation, autoimmune diseases, and suppressing immune response, which encompasses a broad number of diseases or conditions. Furthermore, in claim 9, Applicants are not claiming a method of treating a disease of real-world relevance, they are merely claiming a mechanism. The argument that the diseases claimed by the Applicants are all treated by inhibiting the interaction of LFA-1 with

ICAM-1 and ICAM-3 is insufficient support that the claimed compounds have specific efficacy in current available form for treating all of the disorders and conditions encompassed by the broadly recited claims 9, 26 and 27.

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art without direction, would be unable to treat each and every disease/condition encompassed by claims 9, 26 and 27, using the instant claimed compounds. One of skill in the art would need to determine which diseases/disorders would be benefited by inhibiting the adhesion of LFA-1 to ICAM-1 or ICAM-3, and would furthermore then have to determine whether the claimed compounds would provide treatment of all of the disorders and conditions encompassed by the claims. Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the art would be burdened with undue "experimentation study" to determine whether the claimed compounds not only inhibit the interaction of LFA-1 with ICAM-1 or ICAM-3, but also treat disorders of real-world relevance.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Regarding claim 9, the Examiner recommends including specific diseases and suggests the following language, "A method of inhibiting inflammation for treating _____ or

suppressing immune response in a mammal for treating _____, comprising administering to said mammal...."

Regarding claim 26, the Examiner suggests either combining claim 27 with claim 26, or claiming the possible diseases and conditions that are treated, rather than claiming the mechanism, which is speculative, and recommends the following language, "A method of inhibiting the interaction of LFA-1 with ICAM-1 or ICAM-3 in a mammal, for treating _____ , comprising administering to said mammal a therapeutic amount of a compound according to claim 1."

Regarding claim 27, "inflammatory disease," "allograft rejection," and "reperfusion injury" are acceptable, however the Examiner suggests further limiting the broad terminology also recited, i.e. listing specific diseases within "autoimmune disease" and "tumor metastasis."

Conclusion

9. Claims 1 and 3-27 are pending in the application, claims 9, 26, and 27 are rejected, and claims 1, 3-8, and 10-25 are allowable.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is 571.272.0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Coppins
October 29, 2005

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PRIMARY EXAMINER

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